Patients (or Materials) and Methods: The study was conducted in 12 healthy volunteers. Each patient received a 1-g single dose intravenously of sulbactam, after which PK studies were carried out, using a Monte Carlo simulation to determine the probability of attaining a specific pharmacodynamic target.
Results: The population PKs of sulbactam were; $k12 = 0.637$ (2.003) h-1, $k21 = 0.663$ (1.736) h-1, $k13 = 8.626$ (2.035) h-1, $k31 = 5.424$ (2.058) h-1 $ke = 3.223$ (1.380) h-1, CL = 11.903 (1.978) L/h and $V = 3.693$ (1.434) L. The PTAs for selected regimens over a range of MICs were as follows:

Dosage regimen	MIC (mg/L)	PTA of T>MIC 20% 40%	30%
1 g q8h (1/2/3/4 h infusion)	1	0.17/0.99/0.99/0.99	
	2	0.00/0.21/0.99/0.99	
	4	0.00/0.00/0.44/0.99	
2 g q8h (1/2/3/4 h infusion)	1	0.04/0.99/0.99/0.97	
	2	0.00/0.06/0.99/0.97	
	4	0.00/0.00/0.20/0.97	
3 g q8h (1/2/3/4 h infusion)	4	0.06/0.96/0.88/0.73	
	8	0.00/0.00/0.87/0.73	
4 g q8h (1/2/3/4 h infusion)	4	0.00/0.00/0.02/0.72	
	8	0.43/1.00/0.99/0.99	
3/6/9/12 g q24h (continuous infusion)	4	0.11/0.46/0.99/0.99	
		0.02/0.07/0.66/0.99	
		0.17/0.99/0.99/0.99	
		0.00/0.21/0.99/0.99	

Conclusion: The high PTA (≥90%) achieving 40% T>MIC for an MIC of 8 mg/L was observed when sulbactam was administered by a 4-hour infusion of 3 g q8h, which would be an alternative treatment option for less-susceptible pathogens.
Disclosure of Interest: None declared.

PP211—PIPERINE INCREASES PLASMA DOMPERIDONE CONCENTRATIONS IN THE RAT

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Introduction: Piperine is the main pungent alkaloid present in the fruits of black pepper (Piper nigrum) and long pepper (Piper longum). In traditional medicine, black pepper has been used as an analgesic and anti-inflammatory agent and in the treatment of epilepsy and snake venom poisoning. Piperine also has been reported as an inhibitor against several cytochrome P-450–mediated pathways and Phase II metabolism as well as P-glycoprotein. This study was carried out to investigate the effect of piprine on the pharmacokinetics of domperidone after acute and chronic administration in rats.
Patients (or Materials) and Methods: Animals received a single dose of domperidone (20 mg/kg, p.o.) alone or together with piperine (60 mg/kg, p.o.). Similarly, the same doses of domperidone alone or when it was given together with piperine were administered to rats chronically for 5 days. Plasma samples were collected at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, and 12.0 hours after drug administration. The concentrations of domperidone in the plasma were measured using an HPLC method.
Results: The concomitant administration of piperine with domperidone acutely or chronically resulted in a significant ($P < 0.05$) increase in the maximum plasma concentration (Cmax), the mean area under the plasma concentration–time curve (AUC), and the elimination half-life (t½) of domperidone compared with those obtained for domperidone alone.
Conclusion: The concurrent administration of piprine with domperidone to rats produced a significant increase in the plasma levels of the latter. However, further studies are needed to determine the possible mechanism(s) involved in this pharmacokinetic interaction.
Disclosure of Interest: None declared.

PP212—BIOAVAILABILITY OF DIGOXIN TABLETS, LOW THERAPEUTIC INDEX DRUG, DETERMINED BY EMIT

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Introduction: Introducing of a standard drug monitoring for digoxin, a digitalis glycoside using in heart failure, considerably reduce the incidences of digoxin toxicity. The need for measurement of digoxin concentrations and knowledge about bioavailability of the given preparation arise from the low therapeutic index of digoxin and its concentration-dependent toxicity. The recommended therapeutic range (1.0–2.5 nmol/L) reflects significant increase in the risk of toxicity that occurs with serum concentrations over 2.6 nmol/L. Choosing a proper analytical method for digoxin bioavailability evaluation is essential due to digoxin-like immunologic factor (DLIF) and others interfering substances that overestimate serum digoxin concentration which may be a significant clinical problem.
Patients (or Materials) and Methods: The study was performed on 24 healthy volunteers in accordance with GCP and legal requirements. Digoxin tablets were administered as a single dose of 0.5 mg. Pharmacokinetic profiles were plotted up to 60 hours after dosing. Determination of digoxin concentration in serum samples was performed by immunoenzymatic method by using the Emit® 2000 Digoxin Assay (Siemens Healthcare Diagnostics). EMIT is a homogeneous enzyme immunoassay intended for use in the quantitative analysis of digoxin in human serum or plasma. The method was fully validated according to the international guidelines. Original solutions of digoxin were used as calibration standards. Lower limit of quantification was set at the concentration of 0.1 ng/mL that is sufficient for human pharmacokinetic evaluation. Standard pharmacokinetic and bioavailability parameters in single-dose regiment (AUCt, AUCinf, Cmax, Tmax, MRT, t1/2) were calculated by a noncompartmental method.
Results: Study results, including t1/2 and other bioavailability parameters, were in agreement with the reference data. Mean AUCinf was 33.42 (10.13) ng*h/mL, while AUCt was 23.93 (6.70) ng*h/mL. Cmax was observed as 3.24 (0.77) ng/mL but occurred at different Tmax (range, 0.5–2.5 hours). The intersubject variability was similar in case of AUC and Cmax (range, 23.80%–30.31%). The high variability of Tmax was observed (49.33%). Cmax exceed the recommended therapeutic ranges in most cases due to administration of a high dose of the tested drug. Digoxin tablets elimination half-life in healthy volunteers, even after single dose administration is high (32.78 [6.48] hours) as well as MRT (44.14 [8.34] hours).
Conclusion: The study results have confirmed that the EMIT method was appropriate for assessment digoxin bioavailability and can be used not only as reliable screening test but also in bioavailability and bioequivalence evaluation.
Disclosure of Interest: None declared.

PP213—CORRELATION OF DISSOLUTION DATA WITH CLINICAL EFFICACY OF TWO LAMOTRIGINE TABLET FORMULATION

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Introduction: There are several generic formulations of lamotrigine in Serbia that are widely used in the treatment of patients with epilepsy. The reduction of medical costs with use of generic formulations has potential risk because of the nature of disease, and it is necessary to investigate bioequivalence of each of generic formulations.

Aim: Comparison of the efficacy of the reference and generic formulation of lamotrigine and theinvestigation of lamotrigine serum concentrations variation. Date were compared with in vitro results of dissolution profiles of the reference and generic tablet formulation.

Patients (or Materials) and Methods: Lamotrigine steady-state concentrations were determined by high-performance liquid chromatography. In clinical study 16 patients participated, of whom 9 received reference formulation and 7 patients received generic formulation. Dissolution characteristics were evaluated at 3 points at physiologic pH range (pH 1.2, pH 4.5, pH 6.8), and difference ($f1$) and similarity ($f2$) tests were applied to dissolution data.

Results: The relationship between lamotrigine serum concentration (μg/mL) and lamotrigine dose (mg/kg/d) were linear in both formulations ($r^2 = 0.78484$ original and $r^2 = 0.83417$ generic). There are statistically significant lower lamotrigine serum concentrations in patient treated with original formulation (3.97 [4.1] μg/mL) than those in patients treated with generic formulations (5.78 [2.7] μg/mL). No dose-dependent adverse effects appeared in the patients, though patients treated with generic drug were receiving higher doses due to assumption that they are less potent. Brand drug had a lower standard deviation (SD) and data scattering because, as the dissolution data showed, it is less influenced by pH changes. Further dissolution profiles of 2 formulations were only similar in pH 1.2 medium.

Conclusion: Investigation showed equal efficacy of 2 lamotrigine formulations, and the variations in plasma concentrations are probably due to individual characteristics of patients and differences in liberation rate of drugs in 2 formulations. It can be claimed that even if there are differences in dissolution profiles of 2 drugs they can have equal therapeutic efficacy.

Financial Source: This work has been supported by Ministry of Science and Technology development of Serbia N041012.

Key words: lamotriginedissolution profilegeneric formulation

Disclosure of Interest: None declared.

PP214—TACROLIMUS BLOOD CONCENTRATION IN PATIENTS SUBJECTED TO RENAL TRANSPLANTATION: THE INFLUENCE OF GENDER

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Introduction: Tacrolimus, a potent immunosuppressant, is used for the prevention of allograft rejection in organ transplantation. Tacrolimus trough concentration (TTC) is still widely used as a guide to individualizing tacrolimus dose requirements in renal transplantation. The aim was to investigate the effect of patient's gender on TTC in renal transplant recipients on quaternary immunosuppressive therapy (tacrolimus, mycophenolate mofetil, prednisone, and anti–T lymphocyte globulin).

Patients (or Materials) and Methods: Present retrospective case series study involved 138 male and 70 female patients subjected to renal transplantation. The outpatient examination, recorded in the database of patients from year 2006 to 2008, as the unit of monitoring, contained such 3255 male and 1756 female examinations. Tacrolimus through concentrations were measured by fluorescence polarisation immunoassay (FPIA, TDx, Abbott Laboratories, Chicago, Illinois).

Results: Average TTC in outpatient examinations of male patients (7.098 [3.4870] ng/mL) were significantly higher ($t = 2.432$, $P = 0.015$) compared with female transplant recipients (6.852 [3.2726] ng/mL).In 25.3% of male examinations, TTC were within the "subtherapeutic" range (<5 ng/mL), while 28.3% of female examinations were within the same range; the difference was statistically significant. On the other hand, the number of examinations in which the TTC were "over the therapeutic" range (>10 ng/mL) in females were significantly lower than in males.

TTC (ng/mL)	Tacrolimus Trough Concentration (TTC); No. (%)		*P* value (Chi-square test)
	Male	Female	
<5	824 (25.3)	497 (28.3)	**0.0241**
5–10	1931 (59.3)	1028 (58.5)	0.6101
>10	500 (15.4)	231 (13.2)	**0.0386**
	3255 (100.0)	1756 (100.0)	

Conclusion: Our results indicated TTC as a useful guide in pointing out to potentially relevant influence of sex on its pharmacokinetics, what should be routinely considered and further studied.

Disclosure of Interest: None declared.

PP215—PHARMACOKINETIC STUDY OF GANCICLOVIR (GCV) AFTER SINGLE AND MULTIPLE DOSE IN HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) PATIENTS WITH CYTOMEGALOVIRUS (CMV) INFECTION

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Introduction: Pharmacokinetic data of GCV are limited in HSCT patients under preemptive therapy and its induced hematologic toxicity still problematic.The aim of this study was to evaluate the PK of GCV after single and multiple doses in HSCT patients with CMV infection and to identify correlation between PK parameters and hematologic toxicity.

Patients (or Materials) and Methods: A PK study was conducted between October 2008 and December 2009 at MG hospital in Beirut, after IV GCV treatment in HSCT recipients with CMV infection. CMV disease was recognized by the combination of clinical signs and antigenemia. Patients received 1-hour infusion of 5 mg/kg q 12h for 14 days, and a complete PK study was performed at days 1, 7, and 14. A compartmental and no PK analysis were performed, and plasma GCV was analyzed by an HPLC validated method with UV detection. An ANOVA analysis associated to Freadman test was performed to compare the mean PK parameters. The 95% CI was calculated for some parameters and $P < 0.05$ was considered significant.

Results: Twelve patients were enrolled in this study. A significant difference in creatinine clearance (Clcr) and trombecytopenia,